Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

SARS-CoV-2 vaccine breakthrough infection following a previous infection in a healthcare worker

Dear Editor,

Philomina et al. recently discussed in this journal breakthrough infections in healthcare workers from India.[1] SARS-CoV-2 infections and COVID-19 vaccines have been suggested to elicit immune response and reduce the predisposition to infections as well as severe disease. Reinfections[2] as well as vaccine breakthrough infections,[3] though rare, are now independently documented, but there is a paucity of literature on reinfections in fully vaccinated individuals. Here we describe a 28 year old male healthcare worker who was re-infected after being previously infected with SARS-CoV-2 and after completing the full course of Covishield/ChAdOx1 vaccine.[4]

The patient initially tested positive for SARS-CoV-2 on routine surveillance (TaqPath COVID-19 Combo kit by Thermofisher) with cycle threshold (C_T) values of 22. Subsequently, he developed fever for 2 days, breathlessness which lasted for seven days along with cough, bodyache and sore throat for ten days. On the seventh day of illness the patient suffered a brief drop in the oxygen saturation (SpO2) to 94% which recovered spontaneously on the next day. High-resolution Computed Tomography (HR-CT) revealed no abnormality and the patient tested negative for SARS-CoV-2 on reverse transcription-PCR (RT-PCR). Antibody titres two weeks after testing negative on RT-PCR, revealed a moderate level of antibodies (Elecsys Anti SARS-CoV-2, Roche Diagnostics) to spike protein (12). The patient then proceeded to take the first dose of Covishield/ChAdOx1 vaccine and subsequently the second dose four weeks later. He suffered mild post-vaccine effects including body aches and injection site pain lasting two days after both doses. A month after receiving the second dose, the patient again developed fever and tested positive on RT-PCR (C_T of 13) for SARS-CoV-2.

In the second episode of the infection, the patient had fever for four days, and cough, bodyache, headache, sore throat, loss of smell and taste for twelve days. The SpO2 level was around 94,95%, and the patient had mild difficulty in breathing throughout the symptomatic period. His HR-CT was normal and he had no evidence of primary or secondary immunodeficiencies. The clinical course and timelines are summarised in Fig. 1A and the clinical parameters are summarised in Table 1.

SARS-CoV-2 RNA isolated from the nasopharyngeal specimen of the patient during the post-vaccination episode of infection was taken up for genome sequencing following an amplicon-based COVIDSeq assay (Illumina Inc,) as per the previously described protocol.[5] The sequencing was performed on the Novaseq6000 platform (Illumina Inc.) to generate 100 × 2 base paired end reads. After quality checks, trimmed reads were aligned against the human reference genome (GRCh38). The unmapped reads were extracted and aligned to the SARS-CoV-2 reference genome NC_045512. Mu-

Table 1
Clinical and Biochemical investigations during the course described in the study.

Date	Lab Report	Results / Comments	Reference values
3/09/2020	RT-PCR	Positive	Negative
	Kit: TaqPath COVID-19Combo kit by Thermofisher	Ct value-22	
	C-Reactive Protein	22 mg/l	Upto 5.0 IU/mL
	D-Dimer	459 ng/ml	0–500 ng/ml
	LDH	200 units/l	85–227 U/lit
	High Resolution Computed Tomography (HR-CT)	Normal Score −0/25	0/25
18/09/2020	RT-PCR	Negative	Negative
	Kit: TaqPath COVID-19kit by Thermofisher		
	Neutralising Antibodies	12	
	Kit: Elecsys® Anti-SARS-CoV-2 by Roche		
13/04/2021	RT-PCR	Positive	Negative
	Kit: Covipath COVID-19 RT-PCR kit	Ct value ORF gene-13 Ngene-12 RNasePgene-24	
	C-Reactive Protein	40 mg/l	Upto 5.0 IU/mL
	D-dimer	570 ng/ml	0–500 ng/ml
	High Resolution Computed Tomography (HR-CT)	Normal Score 0/25	0/25

https://doi.org/10.1016/j.jinf.2021.10.008

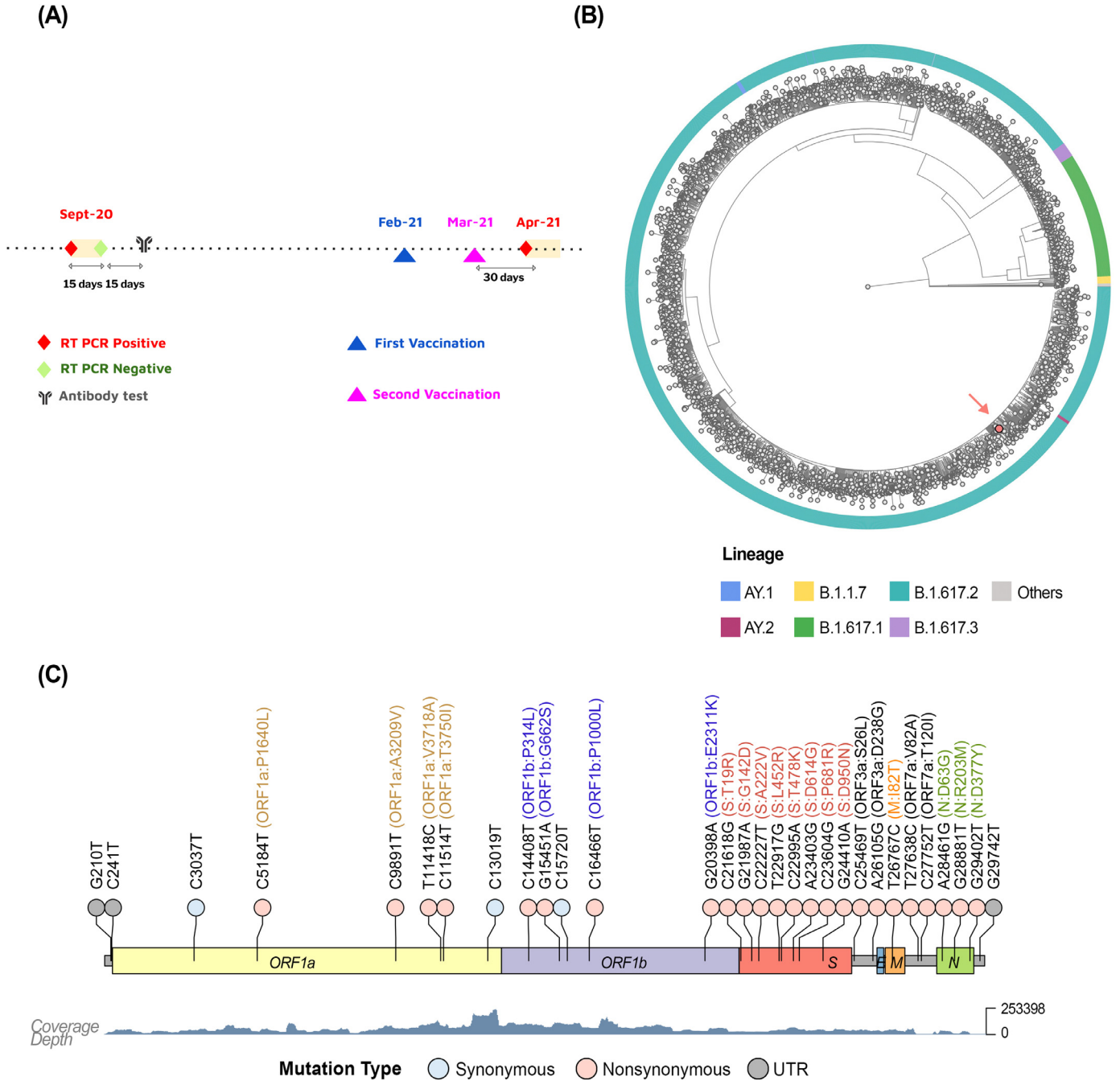

Fig. 1. (A) Summary of timelines and the clinical course for the patient. (B) Phylogenetic context of the genome isolate with other genomes sampled from the state of Maharashtra. (C) Genomic context of the mutations found in the genome isolate.

tations were filtered at a minimum coverage depth of 5 reads and a minimum frequency of 50%. Bases with quality lower than 20 were masked from the consensus sequence. Lineage assignment for the sequence was done using Pangolin (v3.1.11, pangoLEARN version 2021–08–09).[6]

Genome sequence for the viral isolate was assembled at a mean depth of coverage of 30460X, with genome coverage of 99.9%. Genomic analysis suggests the infection was caused by a virus belonging to the lineage B.1.617.2 (Delta) of SARS-CoV-2 (Fig. 1B). The sequence had a total of 30 distinct genetic mutations, 8 of which were in the Spike protein of the virus (Fig. 1C).

While a number of cases of reinfections and vaccine breakthrough infections have been reported, including in healthcare workers, infections following a previous infection and complete course of SARS-CoV-2 vaccines have previously not been documented. We also highlight that variants of concern, especially B.1.617.2 (Delta), have been previously suggested to escape immunity due to previous infections as well as vaccination.[7,8] Both reinfections and vaccine breakthrough infections seem to be enriched in healthcare workers potentially due to their high exposure.[9,10] To the best of our knowledge this is the first report on a combination of both reinfection as well as vaccine breakthrough infection in an individual. This report therefore highlights the need for close follow-up of rare and unusual cases of vaccine breakthroughs as well as reinfections especially in high-risk frontline workers.

Ethics

RNA extracted from nasopharyngeal swab samples were collected as part of routine COVID-19 testing after informed consent as per the institutional ethical committee guidelines (IHEC-CSIR-IGIB/IHEC/2020–21/01).

Funding

Authors acknowledge funding from CSIR India through grant MLP005. Authors BJ AND MKD acknowledges research fellowships from CSIR India. VG and SJA acknowledge research fellowships from University Grants Commission (UGC), India.

Declaration of Competing Interest

Authors declare no conflicts of interest. The funders had no role in the preparation of the manuscript or decision to publish.

References

1. Philomina J B, Jolly B, John N, Bhoyar RC, Majeed N, Senthivel V, et al. Genomic survey of SARS-CoV-2 vaccine breakthrough infections in healthcare workers from Kerala, India. *J Infect* 2021;**83**:237–79.
2. Wang To KK, Hung IFN, Daniel Ip J, Wing-Ho Chu A, Chan WM, Raymond Tam A, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1275.
3. Blachere NE, Hacisuleyman E, Darnell RB. Vaccine breakthrough infections with SARS-CoV-2 variants. reply. *N Engl J Med* 2021;**385**:e7.
4. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;**397**(10269):99–111.
5. Bhoyar RC, Abhinav J, Sehgal P, Kumar Divakar M, Sharma D, Mohamed I, et al. High throughput detection and genetic epidemiology of SARS-CoV-2 using COVID Seq next-generation sequencing. *PLoS ONE* 2021;**16**(2):e0247115.
6. O'Toole A, Scher E, Underwood A, Jackson B, Hill V, T McCrone J, et al. Assignment of epidemiological lineages in an emerging pandemic using the pangolin tool. *Virus Evol* 2021;**7**(2). doi:10.1093/ve/veab064.
7. Delphine P, David V, Artem B, Isabelle S, Florence GB, Michael RM, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. *Nature* 2021;**596**(7871):276–80.
8. Lopez Bernal J, Andrews N, Charlotte G, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021;**385**(7):585–94.
9. Moriah B, Tal G, Yaniv L, Sharon A, Marc L, Carmit C, et al. COVID-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021. doi:10.1056/NEJMoa2109072.
10. Hall Victoria J, Foulkes S, Charlett A, Atti A, Monk JME, Simmons R, et al. SARS–CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet* 2021;**397**(10283):1459–69.

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